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3 INSTRUCTIONS:
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5 **SECTION 1:** Enter your role and association with the CF community.
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7 **SECTION 2:** Review the recommendation statements found in the Table, on
8 pages 18-22 in **Diagnosis_of_CF_Consensus_Guidelines.pdf**. This section
9 includes questions that will ask you to select a recommendation number and
10 provide you with space for comments.
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12 **SECTION 3:** To capture comments and feedback on the body of the
13 manuscript, please select a page number and type in the line number
14 corresponding to your comment and/or suggested change.
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16 **SECTION 4:** To capture comments on the other table and figure you will be
17 prompted to refer to the figure on pages 23-24.
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Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation

by

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ABSTRACT

Background: Cystic fibrosis (CF), caused by mutations in the gene for the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), continues to present diagnostic challenges. Newborn screening and an evolving understanding of CF genetics have prompted a reconsideration of the diagnosis consensus criteria.

Methods: To improve diagnosis and achieve standardized definitions worldwide, the CF Foundation convened a committee of 32 experts in CF diagnosis from 9 countries to develop clear and actionable consensus guidelines on the diagnosis of CF and to clarify diagnostic criteria and terminology for other disorders associated with *CFTR* mutations. An *a priori* threshold of $\geq 80\%$ affirmative votes was required for acceptance of each statement.

Results: After reviewing relevant literature, the committee convened to review evidence and cases. Following the conference, consensus statements were developed by an executive subcommittee. The entire consensus committee voted and approved 27 of 28 statements, 7 of which needed revisions and another round of voting.

Conclusions: It is recommended that diagnoses associated with *CFTR* mutations in all individuals from newborn to adult be established by evaluation of *CFTR* function with a sweat chloride test. The latest mutation classifications annotated in the CFTR2 project (<http://www.cftr2.org/index.php>) should be used to aid in diagnosis. Newborns with a high immunoreactive trypsinogen level and inconclusive *CFTR* functional and genetic testing may be designated *CFTR*-related metabolic syndrome (CRMS) or CF Screen Positive, Inconclusive Diagnosis (CFSPID); these terms are now merged and equivalent, and CRMS/CFSPID may be used. ICD-10 codes for use in diagnoses associated with *CFTR* mutations are included.

250/250 words

INTRODUCTION

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease in the United States, affecting approximately 1 in 4000 newborns in the United States,¹⁻³ and occurring at higher frequencies in some European countries.^{4,5} Cystic fibrosis is a multisystem disorder caused by mutations in the gene for the cystic fibrosis transmembrane conductance regulator (*CFTR*), which encodes an ion channel protein,⁶ with more than 2000 mutations identified to date (<http://www.genet.sickkids.on.ca/cftr/app>⁷).

A diagnosis of CF initially relied on phenotype, with clinical recognition of characteristic signs and symptoms.⁸ (See also Addendum for J Pediatrics Manuscript (MS) #6, which is being drafted.) However, due to widespread CF newborn screening (NBS), at least 64% of new CF diagnoses in the United States now occur in asymptomatic or minimally symptomatic infants following a positive NBS result.⁹ Although the majority of these screen-positive infants can be readily diagnosed with CF after a confirmatory test showing high sweat chloride concentration, the diagnosis is not clear in some individuals,^{10,11} leading to persistent challenges¹² and stresses, and importantly including a potentially disturbed parent/child relationship.¹³⁻¹⁵ Furthermore, universal NBS was implemented only recently in the United States, and many individuals born there prior to 2010 have not been screened. Diagnosis of CF in the nonscreened population can be challenging, because the age of onset and severity of symptoms as a result of *CFTR* dysfunction can be highly variable. Symptoms can include subtle presentations of pancreatitis or respiratory symptoms in older children and adults, nasal polyposis, and male infertility).¹⁶⁻¹⁸ (See also Addendum for J Pediatrics MS #6, which is being drafted.)

The last few years have seen significant growth of phenotypic and genotypic information on CF that can help with interpretation of the disease status in many of these patients. International collection of clinical data from individuals with CF¹⁹ and laboratory advances²⁰ provide functional insight into the physiological impact of the most common mutations (see Addendum for J Pediatrics MS #3, which is being drafted). Due to this new information, and to seek harmony with the diagnostic criteria and terminology²¹ of the European Cystic Fibrosis Society

(ECFS), it was decided that the 2008 diagnostic guidelines²² of the Cystic Fibrosis Foundation (CF Foundation) should be revised.

The CF Foundation convened a committee of 32 experts in the diagnosis of CF from nine countries to update diagnostic guidance and achieve standardization in definitions worldwide. The mission of this committee was to develop clear and actionable consensus guidelines on diagnosis of CF and other conditions associated with mutations in the *CFTR* gene such as CFTR-related metabolic syndrome (CRMS)²³ or CF Screen Positive, Inconclusive Diagnosis (CFSPID),²⁴ and CFTR-related disorder.²⁵ The recommendations in this document address individuals with both clear and unclear diagnosis, including infants with positive NBS and/or prenatal diagnosis (see Addendum for J Pediatrics MS #4, which is being drafted), and individuals with CF-like symptoms who were either never screened or who had false negative newborn or prenatal screening results (see Addendum for J Pediatrics MS #6, which is being drafted). Case studies, designed to show how the recommendations should be applied in challenging clinical scenarios, can be found in additional manuscripts created as a result of this conference, published as Supplement X of *The Journal of Pediatrics* (see Addendum for J Pediatrics MS #3-#6).

METHODS

An international consensus committee of 32 experts was purposively selected and tasked with the development of guidelines on the diagnosis of CF. Committee selection was determined to include participants representative of worldwide CF care communities, particularly pediatric CF providers with NBS experience, and other relevant specialists including adult CF providers. The committee first reviewed the existing CF Foundation diagnosis guidelines,²² a list of

publications on CF diagnosis published since the 2008 CF Foundation Diagnosis Guidelines, and 10 articles selected by conference co-chairs. An executive subcommittee consisting of 10 representatives from 4 countries was established prior to the October 2015 North American CF Conference (NACFC).

The consensus conference was held prior to the 2015 NACFC. At this conference, the committee presented and discussed new studies and data on CF diagnosis. An executive subcommittee developed the consensus statements at subsequent meetings. These statements were reviewed by the consensus committee and voted on by the members using an electronic survey tool (SurveyMonkey).²⁶ Individuals voting against a statement were asked to provide a revised statement or explanation. An *a priori* threshold of $\geq 80\%$ affirmative votes was required for acceptance. Statements that did not reach 80% agreement with the associated committee feedback were reviewed by the committee co-chairs and revised with input from the rest of the executive subcommittee.

After the recommendation statements were agreed upon, they were presented to the European CF Society (ECFS) at the Diagnostic Network Working Group annual meeting in February 2016 to help engage all parties in the discussion. The manuscript was distributed for feedback from the executive subcommittee, conference committee, the CF Foundation's CF Center Committee, all the CF centers in the United States, parents of screened infants, and to a variety of international organizations and their members for a public comment period.

RESULTS AND DISCUSSION

In the survey, participants were able to vote in agreement, disagreement, or to abstain. One committee member did not participate in this vote. Of the 28 statements initially voted on, 8 did not reach at least 80% agreement. The 8 statements that did not pass were reviewed and revised, and reduced to seven statements by the chairs and the executive committee and sent out for a second round of voting. All but one of the 32 committee members participated in this vote. All 7 of the revised statements passed in the second round of voting. For additional detail and a historical perspective please see other articles in the supplement.

The committee approved 27 consensus statements (**Table I**) in 4 overlapping categories that apply to:

1. Both screened and nonscreened populations;
2. Screened pediatric populations, ie, fetuses undergoing prenatal testing and neonates;
3. Infants with uncertain diagnosis and designated either CRMS or CFSPID (now considered to be the same)
4. Patients presenting clinically who represent nonscreened populations, including children born at home or in regions before NBS implementation, those with false negative screening tests, and older individuals.

The **Figure** provides a simplified algorithm for how these consensus statements should be applied to individuals under suspicion of CF. Even though many individuals enter this algorithm through a positive newborn screen in which *CFTR* genetic testing was done, the diagnosis of CF is primarily based on the demonstration of abnormal *CFTR* function by measurement of chloride concentration in the sweat.²² Although obtaining an adequate sweat specimen for chloride measurements can be challenging, particularly in very young infants, experience and studies have shown that this is feasible in full-term infants during the first postnatal month, ie, during the neonatal period.^{27–30} Following the committee’s recommendations, shown below, will improve reliability of the result.

1. All Populations: Sweat chloride testing should be performed according to approved procedural guidelines published in established, international protocols such as the CLSI 2009 Guidelines.

Following appropriate protocols for performing the sweat test²⁸ is important for achieving accurate results and minimizing collection of inadequate amounts of sweat (quantity not sufficient, QNS).^{29–33} (See also Addendum for J Pediatrics MS #4, which is being drafted.)

2. For Newborns: Newborns with a positive CF newborn screen, to increase the likelihood of collecting an adequate sweat specimen, should have the test performed

bilaterally and when the infant weighs > 2 kg, and is at least 36 weeks of corrected gestational age.

Sweat samples collected bilaterally must not be combined; rather, they should be analyzed separately, providing a useful quality control measure.²⁹

3. For Newborns: Newborns greater than 36 weeks gestation and 2 kg body weight with a positive CF newborn screen, or positive prenatal genetic test, should have sweat chloride testing performed as soon as possible after 10 days of age, ideally by the end of the neonatal period (4 weeks of age).

Timing of the sweat chloride test is crucial in newborns.³⁴ Sweat testing can occur as early as 48 hours after birth,²⁵ but most NBS results will not be available by that time. However, testing should occur before the end of the neonatal period because malnutrition and other risks such as dehydration may be present even in the first few weeks of life.^{35–38}

4. For Newborns: In infants with presumptive CF identified through NBS, CF treatment should not be delayed while efforts to establish a diagnosis of CF are initiated.

Optimal outcomes depend on early intervention. Efforts to obtain adequate quantities of sweat and accurate sweat chloride values should not delay start of salt supplementation or other appropriate therapies.³⁹ The CF Foundation recommends that infants with CF have an initial visit at an accredited CF care center within 24-72 hours of diagnosis,³⁹ and timing of the initial visit for infants with a presumptive diagnosis should aim to meet this timeframe. A presumptive diagnosis of CF for purposes of treatment initiation can include the following clinical circumstances:

- A positive CF newborn screen showing 2 CF-causing *CFTR* mutations (see below)
- A positive CF newborn screen AND clinical signs and symptoms of CF
- Meconium ileus, with or without a positive newborn screen.

However, definitive diagnosis requires demonstration of *CFTR* dysfunction.

5. All Populations: Sweat chloride analysis should be performed within a few hours of sweat collection and the results and interpretations should be reported to clinicians and parents or patients, as soon as possible and certainly on the same day.

Prompt reporting should be made regardless of sweat test results.^{40–43} A second, confirmatory, sweat test is not necessary, nor is it likely to be reimbursable; this is a change from previous CF Foundation diagnostic guidelines.^{22,44}

SWEAT CHLORIDE TEST RESULTS ≥ 60 MMOL/L

6. All Populations: In individuals presenting with a positive newborn screen, clinical features consistent with CF, or a positive family history, a diagnosis of CF can be made if the sweat chloride value is ≥ 60 mmol/L.

While the sweat test is commonly used for diagnosis of individuals presenting with symptoms of CF, many newborns are reported as having CF based solely on a positive NBS result. However, NBS tests must always be considered screening procedures and not diagnostic studies. The genetic analysis included as part of many NBS programs must not be relied upon for conclusive diagnosis, as errors can arise from problems with the Guthrie card,⁴⁵ changes in the mutation panel utilized by the NBS program (for example, see ref. 46), or detection of 2 *CFTR* mutations in *cis* (ie, on the same chromosome).⁴⁷ (See also Addendum for J Pediatrics MS #3, which is being drafted.)

7. For Newborns: Individuals who are screen-positive and meet sweat chloride criteria for CF diagnosis should undergo *CFTR* genetic testing if the *CFTR* genotype was not available through the screening process or is incomplete.

Genetic testing is an important part of the diagnostic work-up, and it is not uncommon for a positive NBS result to include the recognition of 2 CF-causing mutations. The screening result should be confirmed in a clinical genetics laboratory, even if a sweat chloride result is positive. The genetic testing results now have additional value in therapy selection.⁴⁸

SWEAT CHLORIDE TEST RESULTS ≤ 29 MMOL/L

8. For Newborns: In individuals with a positive newborn screen, a sweat chloride of less than 30 mmol/L indicates that CF is unlikely.

9. All Populations: Individuals with clinical features that may be consistent with CF who have a sweat chloride less than 30 mmol/L indicates that CF is less likely. It may however be considered if evolving clinical criteria and/or *CFTR* genotyping support CF and not an alternative diagnosis.

Note that the upper limit for a normal sweat chloride is 29 mmol/L for all age groups. This is a change from previous guidelines for people > 6 months of age (the previous upper limit of normal was 39 mmol/L).

See Addendum for J Pediatrics MS #3 (which is being drafted) for more details regarding the diagnosis of CF in the very rare individual with sweat chloride ≤ 29 mmol/L.¹⁹ Some *CFTR* mutations, such as c.3717+12191C>T (legacy name 3849+10kb C->T), are associated with low sweat chloride values; in these cases an alternative diagnosis does not need to be ruled out.^{49,50} (See also Addendum for J Pediatrics MS #6, which is being drafted.)

SWEAT CHLORIDE TEST RESULTS OF 30-59 MMOL/L

10. All Populations: Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30-59 mmol/L) on two separate occasions may have CF. They should be considered for extended *CFTR* gene analysis and/or *CFTR* functional analysis.

Individuals with sweat chloride concentrations in the intermediate range will need further study to establish or rule out a CF diagnosis.^{11,51,52} Evidence may be provided by *CFTR* genotype.¹⁹ (See Addendum for J Pediatrics MS #3, which is being drafted to discuss *CFTR* genetic testing and interpretation in detail) or by further *CFTR* physiologic testing.⁵³⁻⁵⁶ For discussion of demonstration of *CFTR* dysfunction including the use of nasal potential difference (NPD) or intestinal current measurement (ICM) on the screen-positive newborn see Addendum for J Pediatrics MS #4, which is being drafted; see MS #6 for information on the symptomatic patient).

NEXT STEPS FOR INTERMEDIATE SWEAT TEST RESULTS

11. All Populations: The latest classifications identified in the CFTR2 project

[<http://www.cftr2.org/index.php>] should be used to aid with CF diagnosis:

- **CF-causing mutation:** Individuals with 2 copies on separate alleles will likely have CF (clinical sweat confirmation needed)
- **Mutation of varying clinical consequence (MVCC):** a mutation that in combination with a CF-causing mutation or another MVCC mutation may result in CF
- **Uncharacterized mutation/mutation of unknown clinical consequence (UNK):** mutation that has not been evaluated by CFTR2 and may be disease-causing or of variable clinical consequences or benign
- **Non-CF causing mutation:** individuals with 1 or more are unlikely to have CF (as a result of that allele)

The Clinical and Functional Translation of CFTR (CFTR2) project provides a definitive characterization of *CFTR* mutations by collecting clinical and laboratory evidence of phenotypic consequence.¹⁹ For each mutation, the CFTR2 website provides information and classification as listed above. The CFTR2 project is updated as mutation functional analyses are completed. Because mutation categorization may change over time, it is important to confirm genotype interpretation on the most current version of the website.

12. All Populations: In individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, the identification of 2 CF-causing mutations (defined by CFTR2) is consistent with a diagnosis of CF. Sweat chloride testing is necessary, though, to confirm the diagnosis.

As stated above, there are situations in which repeated sweat chloride testing does not provide further clarity, such as in individuals with *CFTR* mutations known to be associated with a normal sweat chloride.^{49,50} (See Addendum for J Pediatrics MS #3, which is being drafted, for further exploration of this topic).

13. All Populations: The absence of detection of 2 CF-causing *CFTR* mutations does not exclude a diagnosis of CF.

Because classification and identification of CF-causing *CFTR* mutations is ongoing, there are individuals with CF in whom 2 *CFTR* mutations have not been detected. Thus, while the CFTR2 initiative has been a valuable step forward in improving the diagnostic characterization of patients with *CFTR* mutations, it does not take the place of clinical observation and expertise. (See Addendum for J Pediatrics Manuscripts #3, #5, and #6, being drafted for more in-depth discussion.)

To further explore a CF diagnosis in individuals with a positive newborn screen, symptoms of CF, or a positive family history, intermediate sweat chloride values (30-59 mmol/L) and fewer than 2 CF-causing mutations, the committee recommends additional CFTR physiological testing. Clinical electrophysiological tests that directly measure CFTR function, such as NPD and ICM may be useful to confirm a diagnosis of CF.⁵⁷

14. All Populations: If further CF functional testing is needed (NPD and ICM), it should be performed in a validated reference center with trained staff certified by the CF Foundation Therapeutics Development Network (TDN) or ECFS Clinical Trial Network (CTN).

When performed correctly, NPD can discriminate between a wide range of CFTR function.⁵⁸⁻⁶⁰ ICM can be used to confirm a diagnosis of CF in the context of intermediate sweat chloride levels,^{55,56,60-63} and may be useful when NPD testing is unsuccessful (for example, when attempting to conduct NPD testing in the uncooperative child).⁶⁴ (See also Addendum for J Pediatrics MS #4, which is being drafted.)

15. For Newborns: In individuals with a positive newborn screen but variable or uncharacterized *CFTR* mutations (<2 CF-causing mutations), the diagnosis of CF can be made by demonstrating CFTR dysfunction (a sweat chloride \geq 60 mmol/L or CF-typical NPD or ICM).

FOR THE NEWBORN WITH AN INCONCLUSIVE DIAGNOSIS

16. For Newborns: The term CRMS is used in the United States for health care delivery purposes and CFSPID is used in other countries, but these both describe an inconclusive diagnosis following NBS.

Newborn infants with a high level of immunoreactive trypsinogen (IRT) and inconclusive CFTR functional and genetic testing may be labelled either CRMS²³ or CFSPID.²⁴ (See also Addendum for J Pediatrics MS #5, which is being drafted.) CFSPID describes the inconclusive nature of the condition in a manner that is easy for patients and families to understand and can be designated by ICD-10 code P09. However, due to US health care system requirements (see Addendum for J Pediatrics MS #2, which is being drafted), CRMS (ICD-10 code E88.89) must be used in clinical settings of the USA for continuing, follow-up care. These two terms are nearly identical, and the Consensus Committee recommends that the two terms be harmonized, for improved international communications and analysis of clinical outcomes. The term CRMS/CFSPID will be used throughout this supplement and is recommended.⁶⁵

17. For Newborns: The term CRMS/CFSPID is reserved for screen-positive individuals without clinical features consistent with a diagnosis of CF.

The CRMS/CFSPID diagnosis should not be used in other clinical scenarios, including those involving individuals who have not received a positive NBS result, or individuals who have clinical symptoms attributable to CFTR dysfunction (see Addendum for J Pediatrics MS #6, which is being drafted).

18. For Newborns: The definition of CRMS/CFSPID is an infant with a positive NBS test for CF and either:

- A sweat chloride value less than 30 mmol/L and 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences
- OR
- An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations

Individuals designated as CRMS/CFSPID should be seen at an accredited CF care center to ensure there are no hidden signs or symptoms of CF and to establish a plan for follow-up.^{23,66}

NEXT STEPS IN THE NEWBORN WITH CRMS/CFSPID DESIGNATION

(For detailed information see Addendum for J Pediatrics MS #5.)

19. For Newborns: Children designated as CRMS/CFSPID should undergo at least one repeat sweat chloride test at CF centers with suitable expertise, such as an accredited CF center.

This test should be used to confirm the CRMS/CFSPID designation. Appropriate timing for the repeat sweat chloride test is discussed in J Pediatrics MS #5 (being drafted; see Addendum).

20. For Newborns: Children designated as CRMS/CFSPID should have clinical evaluation performed by CF providers to identify the minority that may develop clinical symptoms.

21. For Newborns: Children designated as CRMS/CFSPID can be considered for extended *CFTR* gene analysis (sequencing and or deletion duplication testing), as well as *CFTR* functional analysis (NPD/ICM) testing to further define their likelihood of developing CF.

22. For Newborns: The decision to reclassify children designated as CRMS/CFSPID as CF is an integrated decision that should take into account functional assessment of *CFTR* (sweat chloride, and possibly NPD/ICM), *CFTR* genetic analysis, and clinical assessment by the CF clinicians caring for the patient.

The decision to change a designation from CRMS/CFSPID to CF is a difficult one and should be made by an experienced CF physician.^{23,24} (See also Addendum for J Pediatrics MS #5, which is being drafted.) Monitoring symptoms, surveillance evaluations (respiratory tract cultures, imaging, and spirometry or lung-clearance index when age-appropriate), and measuring fecal elastase levels or following IRT or

pancreatitis associated protein (PAP) trends may be considered if clinically indicated and to objectively identify CF clinical manifestations (phenotypes).^{10,23,54,56,66–68} CF cannot be diagnosed through the identification of elevated levels of IRT, which can occur in the context of other tissue stress.^{69,70}

23. For Newborns: Genetic counseling should be offered to families of individuals followed for CRMS/CFSPID, including a discussion of the risk in future pregnancies.

Our understanding of the impact of various *CFTR* mutations is evolving and will continue to be clarified for many years. Genetic counseling is important for parents to understand the risk of a child having CF or being designated as CRMS/CFSPID in future pregnancies.^{23,24}

24. For Newborns, Research Recommendation: Infants with a designation of CRMS/CFSPID (by definition) do not have clinical features consistent with a diagnosis of CF and further research is needed to determine the prognosis and best practices for frequency and duration of follow up.

There is inadequate evidence to recommend a standard period and frequency for follow-up of these individuals. Further research on this will require common definitions, and the merging of CRMS and CFSPID designations is therefore especially timely.

GENERAL NOTE FOR THE NONSCREENED INDIVIDUAL

25. For individuals presenting with CF symptoms, the same diagnostic criteria recommended for the screened population for sweat chloride testing, *CFTR* genetic analysis, and *CFTR* functional testing should be used to confirm a CF diagnosis.

Although NBS encompasses the majority of new diagnoses, diagnosis of CF in the nonscreened population, particularly those born before the initiation of NBS at all accredited CF centers, still occurs. In these individuals, the diagnostic algorithm (**Figure**) remains applicable. However, the assignment of a diagnosis of CF will be weighed against alternative diagnostic explanations of the presenting symptom or feature. Therefore, the pre-test probability will influence the interpretation of sweat chloride testing, *CFTR* genetic analysis, or *CFTR* physiologic testing.

Definitive diagnostic criteria for nonscreened populations include the presence of CF symptoms
OR a family history and:

- Sweat chloride ≥ 60 mmol/L
- OR
- The presence of 2 CF-causing *CFTR* mutations
- OR
- Physiologic testing demonstrating *CFTR* dysfunction.

The diagnosis of CF can also be appropriate if the above testing is not definitive, but *CFTR* dysfunction is the best explanation of the patient's symptoms, and CF therapies would improve the patient's condition.

FOR THE NONSCREENED INDIVIDUAL WITH THE INCONCLUSIVE DIAGNOSIS

There are scenarios in which a given patient may not meet the above diagnostic criteria to be diagnosed with CF, but also cannot be “ruled-out” as not having CF. Though this situation is similar to infants with CRMS/CFSPID, those classifications are not appropriate for the nonscreened populations.

26. The diagnosis of *CFTR*-related disorder has been defined as a monosymptomatic clinical entity [CBAVD/pancreatitis/bronchiectasis] associated with *CFTR* dysfunction that does not fulfill the diagnostic criteria for CF.

Individuals with a monosymptomatic *CFTR*-related disorder²⁵ should be assessed and followed by a CF physician. (See Addendum for J Pediatrics MS #6, which is being drafted.)

27. Clinicians should avoid the use of terms like classic/nonclassic CF, typical/atypical CF, delayed CF, since these terms have no harmonized definition and could be confusing for families or caregivers.

In these and other situations, education on clinical entities and organ pathologies associated with CF and their relationship with *CFTR*-related disorder, should be provided to patients, families, and primary care providers to aid in the early recognition of symptoms of CF.

ICD-10 CODES FOR INDIVIDUALS WITH *CFTR* DYSFUNCTION

The International Statistical Classification of Diseases and Related Health Problems (ICD)⁷¹ system is a medical classification list created collaboratively by the World Health Organization (WHO) to be “the international standard for defining and reporting diseases and health conditions. It allows the world to compare and share health information using a common language.”⁷² It is an alphanumeric system containing codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases. The ICD system is valuable, indeed essential, for many purposes including: 1) entry and continuation into the healthcare delivery mechanisms of some countries such as the United States where the ICD codes are an integral and required component of billing; 2) coding death certificates internationally, thus allowing assessment of mortality data; 3) epidemiologic research; and 4) medical economics research.

The most recent revision of the system, ICD-10, implemented in October 2015, provides more than 14,400 different codes and can be expanded to over 16,000 codes by using optional sub-classifications. It is not possible to convert ICD-9 datasets to ICD-10. In the ICD-10 coding system, characters 1-3 indicate the category of disease; 4-6 indicate etiology, anatomic site, severity or other clinical detail of disease; and character 7 is a placeholder for extending the code to increase specificity. The designation “E” indicates endocrine, nutritional and metabolic diseases, while “J” applies to diseases of the respiratory system.

Some CF specialists were engaged in the ICD-10 development process but the degree of influence was limited, and coding for diseases or disorders caused by CFTR dysfunction is not ideal, including the absence of a code for CFTR-related disorder (CFTR-RD). The current ICD-10 code is undergoing revision to ICD-11, which is due to be completed in 2018. Participation is invited (<http://www.who.int/classifications/icd/revision/en/>), and we encourage involvement by CF caregivers.

A list of ICD-10 codes that should be used in the delivery of care for those disorders associated with *CFTR* mutations (that is, CF, CRMS/CFSPID, and CFTR-related disorder) is shown in Table II.

CONCLUSION

Although newborn screening is now widely implemented, the diagnosis of CF is not always clear. A sweat test is required for confirmation of CF; a sweat chloride level ≥ 60 mmol/L indicates a diagnosis of CF and a sweat chloride level < 30 mmol/L indicates that CF is unlikely. In individuals who fall into the intermediate sweat chloride level, 30-59 mmol/L, genetic analysis is required. Further testing for CFTR function such as NPD and ICM may also be indicated but need to be performed in a specialized center approved for such studies. Some individuals with sweat chloride levels from 30-59 mmol/L or even ≤ 29 mmol/L and inconclusive genetic testing may also be designated as CRMS/CFSPID due to the results of NBS, but further research is needed to determine their prognosis, best practice, and frequency of follow-up.

Table I: Consensus Recommendations for Diagnosis of Cystic Fibrosis

	Statements	Vote	Abstain (n)
1	Sweat chloride testing should be performed according to approved procedural guidelines published in established, international protocols such as the CLSI 2009 Guidelines.	100%	0
2	Newborns with a positive CF newborn screen, to increase the likelihood of collecting an adequate sweat specimen, should have the test performed bilaterally and when the infant weighs > 2 kg, and is at least 36 weeks of corrected gestational age.	87%	0
3	Newborns greater than 36 weeks gestation and 2 kg body weight with a positive CF newborn screen, or positive prenatal genetic test, should have sweat chloride testing performed as soon as possible after 10 days of age, ideally by the end of the neonatal period (4 weeks of age).	93%	1
4	In infants with presumptive CF identified through NBS, CF treatment should not be delayed while efforts to establish a diagnosis of CF are initiated.	83%	1

5	Sweat chloride analysis should be performed within a few hours of sweat collection and the results and interpretations should be reported to clinicians and parents or patients, as soon as possible and certainly on the same day.	90%	0
6	In individuals presenting with a positive newborn screen, clinical features consistent with CF, or a positive family history, a diagnosis of CF can be made if the sweat chloride value is ≥ 60 mmol/L.	93%	0
7	Individuals who are screen-positive and meet sweat chloride criteria for CF diagnosis should undergo <i>CFTR</i> genetic testing if the <i>CFTR</i> genotype was not available through the screening process or is incomplete.	100%	0
8	In individuals with a positive newborn screen, a sweat chloride of less than 30 mmol/L indicates that CF is unlikely.	82%	2
9	Individuals with clinical features that may be consistent with CF who have a sweat chloride less than 30 mmol/L indicates that CF is less likely. It may however be considered if evolving clinical criteria and/or <i>CFTR</i> genotyping support CF and not an alternative diagnosis.	80%	0
10	Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30-59 mmol/L) on two separate occasions may have CF. They should be considered for extended <i>CFTR</i> gene analysis and/or <i>CFTR</i> functional analysis.	90%	0
11	<p>The latest classifications identified in the CFTR2 project [http://www.cftr2.org/index.php] should be used to aid with CF diagnosis:</p> <ul style="list-style-type: none"> • CF-causing mutation: Individuals with 2 copies on separate alleles will likely have CF (clinical sweat confirmation needed) 	100%	0

	<ul style="list-style-type: none"> • Mutation of varying clinical consequence (MVCC): a mutation that in combination with a CF-causing mutation or another MVCC mutation may result in CF • Uncharacterized mutation/mutation of unknown clinical consequence (UNK): mutations that have not been evaluated by CFTR2 and may be disease-causing or of variable clinical consequences or benign • Non-CF causing mutation: individuals with 1 or more are unlikely to have CF (as a result of that allele) 		
12	In individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, the identification of 2 CF-causing mutations (defined by CFTR2) is consistent with a diagnosis of CF. Sweat chloride testing is necessary, though, to confirm the diagnosis.	87%	0
13	The absence of detection of 2 CF-causing CFTR mutations does not exclude a diagnosis of CF.	93%	1
14	If further CF functional testing is needed (NPD and ICM), it should be performed in a validated reference center with trained staff certified by the CF Foundation Therapeutics Development Network (TDN) or ECFS Clinical Trial Network (CTN).	100%	0
15	In individuals with a positive newborn screen but variable or uncharacterized <i>CFTR</i> mutations (<2 CF-causing mutations), the diagnosis of CF can be made by demonstrating CFTR dysfunction (a sweat chloride \geq 60 mmol/L or CF-typical NPD or ICM).	93%	0
16	The term CRMS is used in U.S. for health care delivery purposes and CFSPID is used in other countries, but these both describe an inconclusive diagnosis following NBS.	96%	2

17	The term CRMS/CFSPID is reserved for screen- positive individuals without clinical features consistent with a diagnosis of CF.	83%	1
18	<p>The definition of CRMS/CFSPID is an infant with a positive NBS test for CF and either:</p> <ul style="list-style-type: none"> • A sweat chloride value less than 30 mmol/L and 2 <i>CFTR</i> mutations, at least 1 of which has unclear phenotypic consequences <p>OR</p> <ul style="list-style-type: none"> • An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations 	86%	1
19	Children designated as CRMS/CFSPID should undergo at least one repeat sweat chloride test at CF centers with suitable expertise, such as an accredited CF center.	86%	1
20	Children designated as CRMS/CFSPID should have clinical evaluation performed by CF providers to identify the minority that may develop clinical symptoms.	83%	1
21	Children designated as CRMS/CFSPID can be considered for extended <i>CFTR</i> gene analysis (sequencing and or deletion duplication testing), as well as <i>CFTR</i> functional analysis (NPD/ICM) testing to further define their likelihood of developing CF.	80%	0
22	The decision to reclassify children designated as CRMS/CFSPID as CF is an integrated decision that should take into account functional assessment of <i>CFTR</i> (sweat chloride, and possibly NPD/ICM), <i>CFTR</i> genetic analysis, and clinical assessment by the CF clinicians caring for the patient.	90%	0
23	Genetic counseling should be offered to families of individuals followed for CRMS/CFSPID, including a discussion of the risk in future pregnancies.	100%	1

24	<i>Research Recommendation:</i> Infants with a designation of CRMS/CFSPID (by definition) do not have clinical features consistent with a diagnosis of CF and further research is needed to determine the prognosis and best practices for frequency and duration of follow up.	96%	0
25	For individuals presenting with CF symptoms, the same diagnostic criteria recommended for the screened population for sweat chloride testing, <i>CFTR</i> genetic analysis, and <i>CFTR</i> functional testing should be used to confirm a CF diagnosis.	93%	0
26	The diagnosis of <i>CFTR</i> -related disorder has been defined as a monosymptomatic clinical entity [CBAVD/pancreatitis/bronchiectasis] associated with <i>CFTR</i> dysfunction that does not fulfill the diagnostic criteria for CF.	86%	2
27	Clinicians should avoid the use of terms like classic/nonclassic CF, typical/atypical CF, delayed CF, since these terms have no harmonized definition and could be confusing for families or caregivers.	83%	1

TABLE II. ICD-10 Codes for Use in Individuals with Cystic Fibrosis and other CFTR Dysfunctional Diseases or Disorders.

Disease/Disorder	Primary ICD-10 Code	Secondary ICD-10 Code
Cystic fibrosis, unspecified	E84.9	
Cystic fibrosis, with meconium ileus	E84.11	
Cystic fibrosis, with other intestinal manifestations (eg, distal intestinal obstruction syndrome (DIOS))	E84.19	
Cystic fibrosis, with pulmonary manifestations	E84.0	Use secondary code for details such as infectious organisms present (eg, B96.5 for <i>Pseudomonas aeruginosa</i>)
Cystic fibrosis, with acute pneumothorax	E84.09	J93.83
Cystic fibrosis, with pneumothorax not otherwise specified	E84.09	J93.9
Cystic fibrosis, with hemoptysis	E84.09	R04.2
CRMS, metabolic disorder unspecified	E88.89	
CFSPID	P09 (abnormal findings on neonatal screening)* Or: E88.89 (if CRMS/CFSPID is adopted as the preferred terminology)	
CFTR-related disorder (Code the signs/symptoms as described but do NOT use E84.9) Pancreatitis, recurrent CBAVD Bronchiectasis, chronic acquired	K85.9 Q55.4** J47.9	} Z14.1 (Cystic fibrosis carrier status)

*Describes positive newborn screen result with an inclusive diagnosis but only applies to the newborn period and thus cannot be used in follow-up care

**Preferred over N46.025 (azoospermia due to a systemic disease)

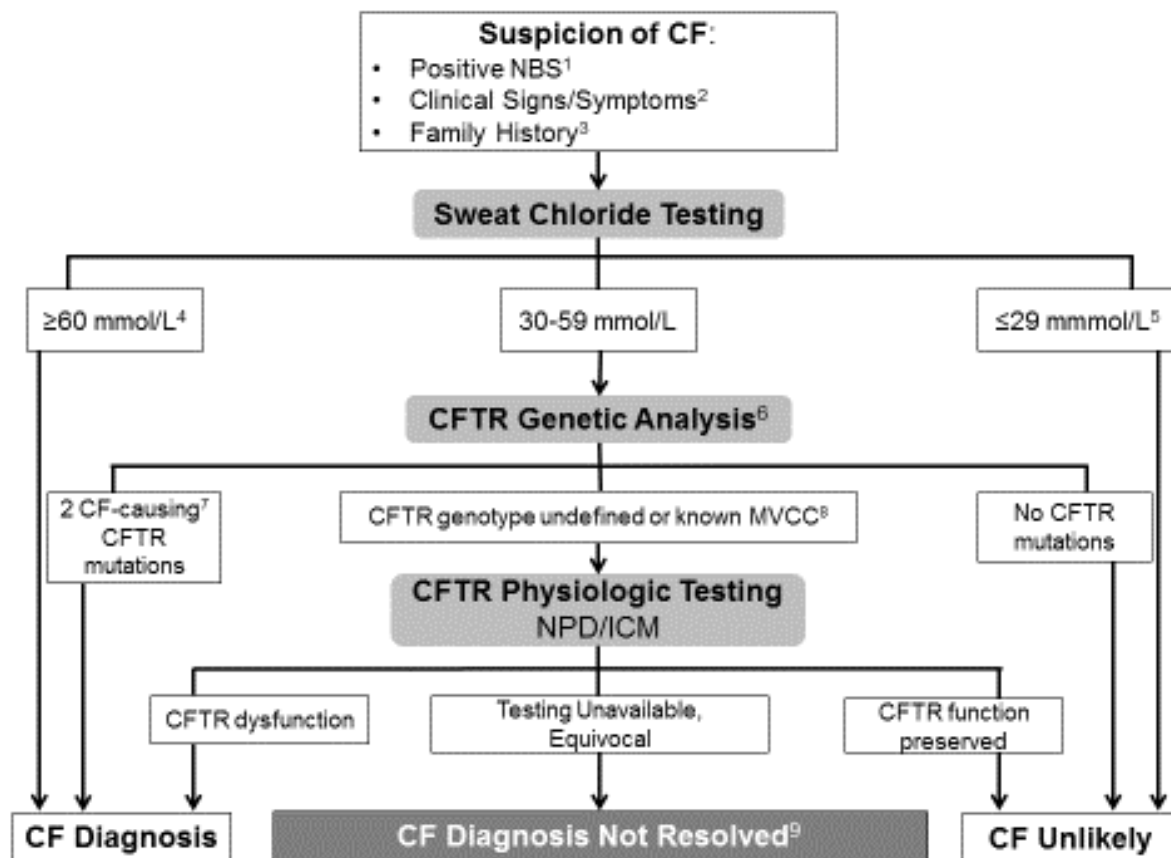


Figure. Recommended Pathway for Diagnosis of Cystic Fibrosis.

Notes:

1. A positive newborn screen may include *CFTR* genetic analysis. (See also Addendum for J Pediatrics MS #4, which is being drafted.) Even though the genetic analysis may be done first, to establish the diagnosis of CF, sweat chloride testing is the first test to be considered.
2. Clinical symptoms refer to nonscreened patients. (See also Addendum for J Pediatrics MS #6.)
3. Family history refers to a 1st degree relative with CF (parent, child, sibling).
4. All individuals with a CF diagnosis should undergo genotyping.
5. Rare individuals may have CF with a sweat chloride below the intermediate range. (19) CF may still be considered as a diagnosis if alternatives are excluded and other confirmatory tests (genotype, physiologic testing) support CF. (See also Addendum for J Pediatrics MS #3).
6. CF-causing as defined by CFTR2 group. (19) For further details and discussion see Addendum for J Pediatrics MS #3.
7. Genetic analysis that reveals *CFTR* variants, but cannot be classified as a CF-causing genotype. If genetic analysis is limited, and especially if only one *CFTR* variant is identified, further *CFTR* testing (such as sequencing, deletion/duplication detection) should be performed. (See also Addendum for J Pediatrics MS #3.)
8. The absence of any CF-causing mutation, or mutation of varying clinical consequence (MVCC), or undefined *CFTR* variants makes CF unlikely. Variants that are known to be non-CF-causing are not considered to be *CFTR* variants for purposes of diagnosis.
9. CF diagnosis not resolved is meant to consider alternative characterizations such as CRMS/CFSPID in the case of NBS; *CFTR*-related disorder in appropriate circumstances. In many instances no distinct label may be appropriate, but further follow-up may be warranted. In these cases, the use of “CF carrier” or the specific clinical problem should be used for characterization/labeling purposes.

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ADDENDUM 1

References to manuscripts being drafted for submission to *The Journal of Pediatrics* as part of the supplement entitled "*Diagnosis of Cystic Fibrosis: Consensus Guidelines and Supporting Evidence from the Cystic Fibrosis Foundation 2015 Diagnosis Consensus Conference.*" (Titles and authorship may not be final; responsible authors are denoted in bold type.)

MS # 1. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation (this manuscript)

MS # 2. Cystic Fibrosis Diagnostic Challenges over Four Decades: Historical Perspectives and Lessons Learned
(**P. Farrell**, T. White, B. Rosenstein and N. Derichs)

MS # 3. Applying *CFTR* Genetics and CFTR2 Data to Facilitate Diagnoses
(**P. Sosnay**, C. Castellani and D. Salinas)

MS # 4. Diagnosis of Cystic Fibrosis in Screened Populations
(**P. Farrell**, T. White, M. Howenstine, A. Munck, R. Parad, M. Rosenfeld, O. Sommerberg, F. Accurso, and J. Davies)

MS # 5. CFTR-Related Metabolic Syndrome and Cystic Fibrosis Screen Positive, Inconclusive Diagnosis
(**C. Ren**, K. Southern, M. Howenstine, A. Munck, I. Sermet, and D. Borowitz)

MS # 6. Diagnosis of Cystic Fibrosis in Nonscreened Populations
(**P. Sosnay**, N. Derichs, and J. Nick)

ADDENDUM 2 [revisions to the 2008 consensus guidelines for diagnosis]:

- Sweat testing should be done in everyone, including all NBS+ infants
- Sweat Cl normal threshold is 30 mmol/L for all ages
- NPD/ICM should be done in a validated lab
- Use the CFTR2 classification of CFTR mutations
- CRMS=CFSPID → Harmonized definition
- Presumptive Dx of CF can be made in NBS+/2 mutation infant
- Non screened population with non-diagnostic sweat Cl
 - Extended genetic analysis
 - Ancillary testing NPD/ICM
- CRMS/CFSPID
 - Repeat sweat testing up to 2 y/o
 - Extended genetic analysis is recommended

- 829 ○ Duration and frequency of follow up remains undetermined
- 830 ○ Conversion to a CF Dx is a clinical decision
- 831 • Other definitions
- 832 ○ Avoid terms like “atypical” or “nonclassical” CF since there is no consensus
- 833 definition of these terms
- 834 ○ CFTR Related Disorder: A monosymptomatic entity that does not meet diagnostic
- 835 criteria for CF

DRAFT